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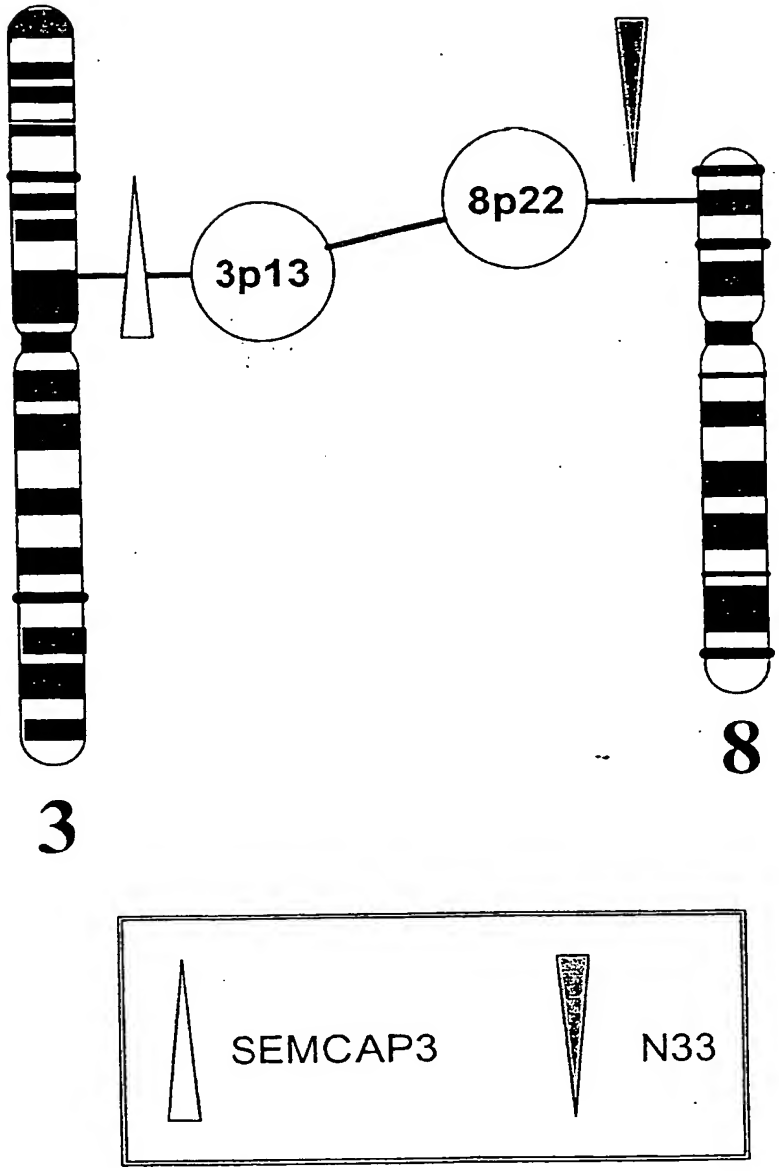

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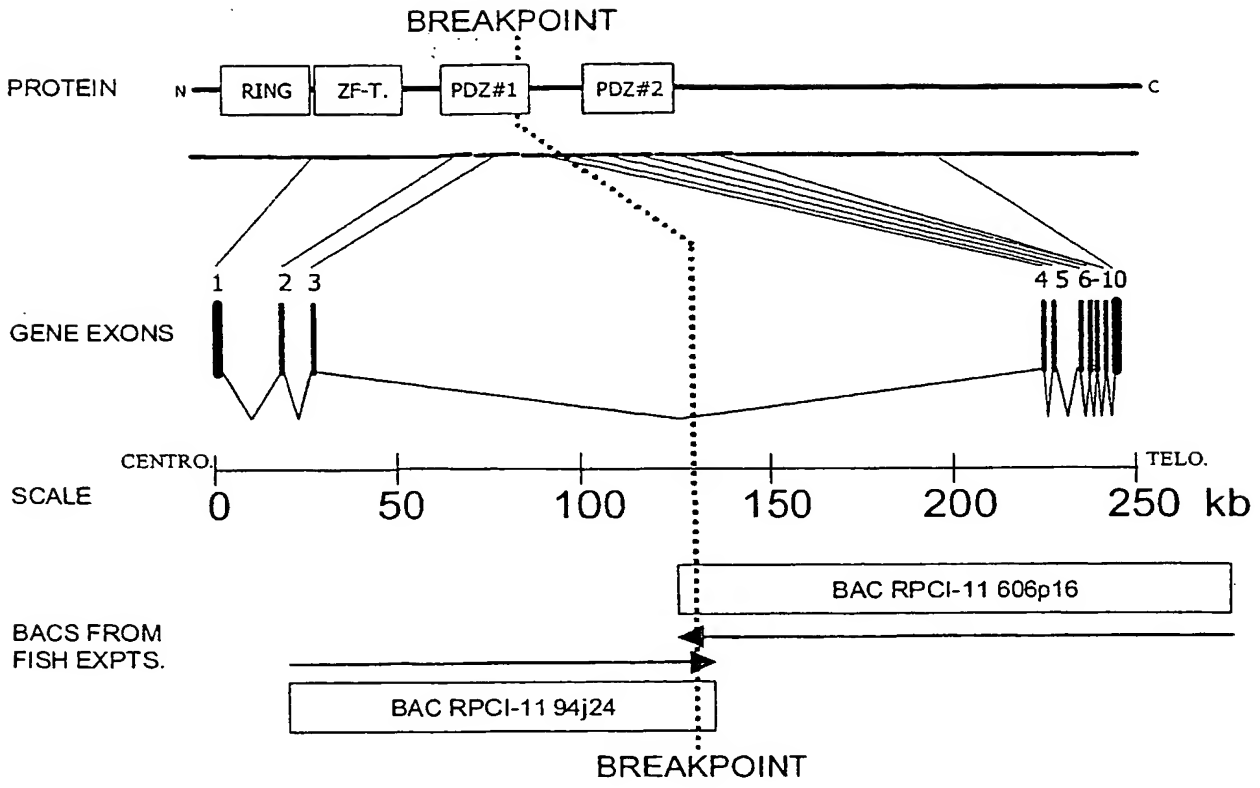
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BREAKPOINT

Figure 3

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 241 TTGATCCGTT CGGGAAGGGG CTCGAAGAGA ACCCTTGGGA GAAAGCAGTA GCCTCAGCTC
 301 CAAACTCAGC GAGCTTTTCT CGGCTGGCGT TTTGTCTCCT ATAGCGTAGA CTGTAAGAGA
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Figure 4

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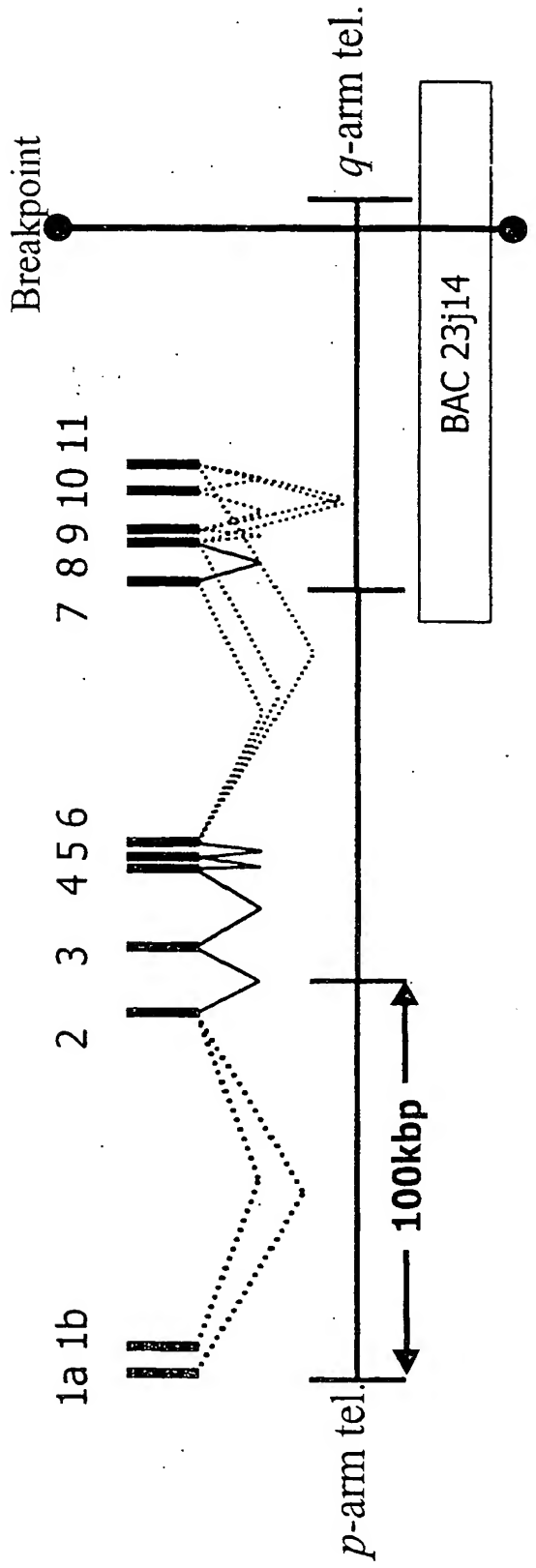
Figure 5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2 3 4 5 6
1a 1b
100kbp
p-arm tel.

Figure 6

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1b
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2-6
These exons have been joined together as they are always spliced in this way.
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actga

8
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8+
This is identical to 8 except a cryptic splice acceptor upstream is employed.
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Figure 7

Alternative start exons

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1b:

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Transcript options

2-6,7,8,9,10,11

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tgaattc

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EWSSRRSIFRMNGDKFRKFIKAPPRNYSMIVMFTALQPQRQCSVCRQANEEYQILANSW
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SLCIVFAMTSGQMWNHIRGPPYAHKNPHNGQVFNHSGTLCSEPEKLIDFIHIYVYGFLD
NYCRCRYHHGDGSSK

2-6,8+,11
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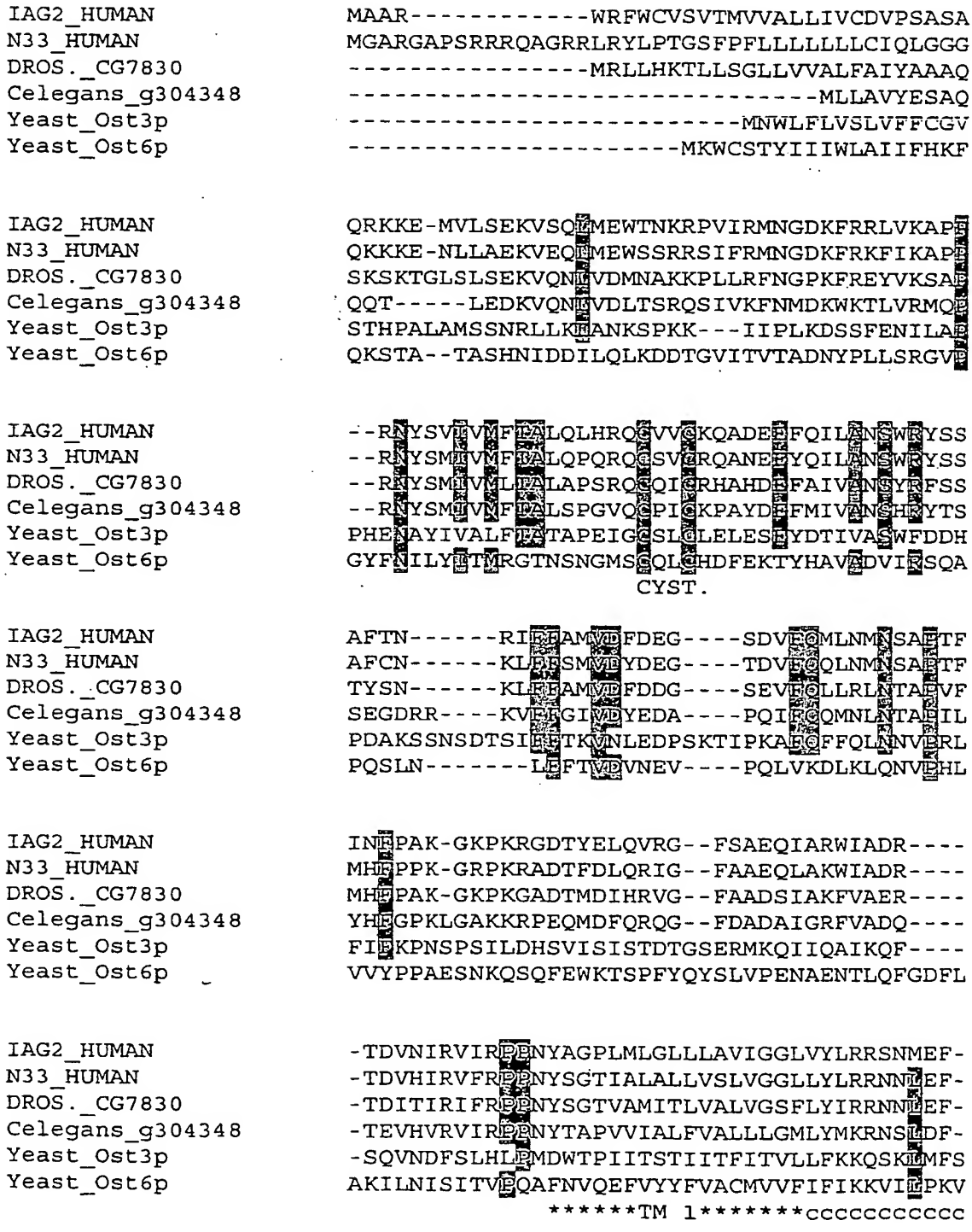
Figure 8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CYST.
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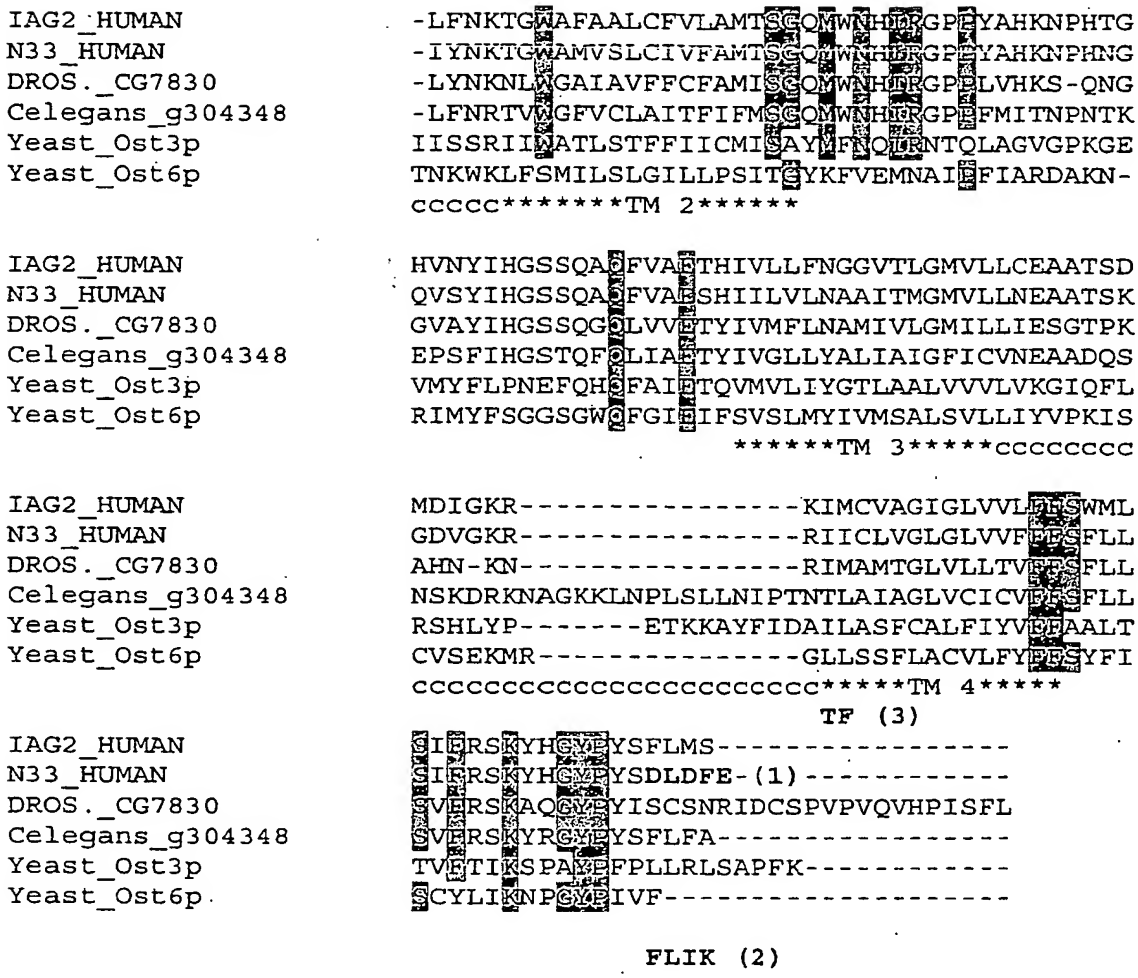
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Celegans_g304348
Yeast_Ost3p
Yeast_Ost6p
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GDVGKR----------RIICLVGLGLVVF
AHN-KN----------RIMAMTGLVLLTV
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RSHLYP-------ETKKAYFIDAILASFCALFIYV
CVSEKMR----------GLLSSFLACVLFY
cccccccccccccccccccccc*****TM 4*****
TF (3)
SIFRSKYHGVPYSFLMS----------
SIFRSKYHGVPYSDLDFE-(1)----------
SVFRSKAQGVPYISCSNRIDCSPVPVQVHPISFL
SVFRSKYRGVPYSFLFA----------
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SCYLIKNPGVPIVF----------
FLIK (2)

Figure 9

C-termini of N33 splice forms

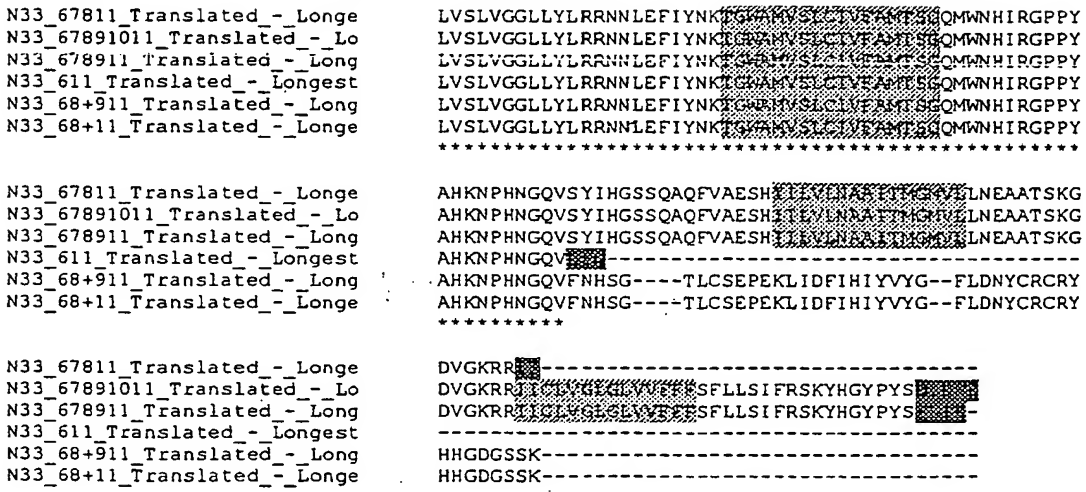

Figure 10

Published GRIK4 nucleic acid sequence (accession NM_014619).

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  61 agcccgcact ccttgaggat cgctgctatc ttggacgacc ccatggagtg cagcagaggg
 121 gagcggctct ccatcaccct ggccaagaac cgcatcaacc gcgctcctga gaggctgggc
 181 aaggccaagg tcgaagtgga catctttgag cttctcagag acagcgagta cgagactgca
 241 gaaaccatgt gtcagatcct ccccaagggg gtggtcgctg tcctcggacc atcgtccagc
 301 ccagcctcca gctccatcat cagcaacatc tgtggagaga aggaggtccc tcacttcaaa
 361 gtggccccag aggagttcgt caagttccag ttccagagat tcacaaccct gaacctccac
 421 cccagcaaca ctgacatcag cgtggctgta gctgggatcc tgaacttctt caactgcacc
 481 accgcctgcc tcatctgtgc caaagcagaa tgcctttaa acctagagaa gctgctccgg
 541 caattcctta tctccaagga cacgctgtcc gtccgcatgc tggatgacac ccgggacccc
 601 accccgctcc tcaaggagat ccgggacgac aagaccgcca ccatcatcat ccacgccaac
 661 gcctccatgt cccacaccat cctcctgaag gcagccgaac ttgggatggt gtcagcctat
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 781 gatcgtgtca acatcctggg attttccatt ttcaaccaat cccatgcttt cttccaagag
 841 tttgcccaga gcctcaacca gtcctggcag gagaactgtg accatgtgcc cttcactggg
 901 cctgcgctct cctcggccct gctgtttgat gctgtctatg ctgtggtgac tgcggtgcag
 961 gaactgaacc ggagccaaga gatcggcgtg aagcccttgt cctgcggctc ggcccagatc
1021 tggcagcacg gcaccagcct catgaactac ctgcgcatgg tagaattgga aggtcttacc
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1201 gacagccacc tctatgcctc caacatctcg gacactctct tcaacaccac cctggtcgtc
1261 accaccatcc tggaaaaccc atatttaatg ctgaagggga accaccagga gatggaaggc
1321 aatgaccgct acgagggctt ctgtgtggac atgctcaagg agctggcaga gatcctccga
1381 ttcaactaca agatccgcct ggttggggat ggcgtgtacg gcgttcccga ggccaacggc
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1561 ggaattagca ttctttaccg cattcatatg ggacgcaaac ccggctattt ctccttcctg
1621 gacccatttt ctccgggcgt ctggctcttc atgcttctag cctatctggc cgtcagctgt
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1861 gtcagtggcg tctggtgggc attcacgctg atcatcatct catcctacac ggccaacctg
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1981 gaccagaccg ccattgaata tggcacaatt cacggaggct ccagcatgac cttcttccaa
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2521 gtctgccagg agatggtgac cgagctgcgc agcattatcc tgtgtcagga cagtatccac
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2701 ctcgcgcaga gactggcgca ggaggccgcc ctggtggccc gcggctgcac gcacatccgc
2761 gtctgccccg agtgccgccg cttccagggc ctgcgggcac ggccgtcgcc cgcccgcagc
2821 gaggagagcc tggagtggga gaaaaccacc aacagcagcg agcccgagta g
```

Figure 11

Published GRIK4 protein sequence (accession NP_055434).

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FKVAPEEFVKFQFQRFTTLNLHPSNTDISVAVAGILNFFNCTTACLICAKAECLLNLEK
LLRQFLISKDTLSVRMLDDTRDPTPLLKEIRDDKTATIIIHANASMSHTILLKAAELGM
VSAYYTYIFTNLEFSLQRTDSLVDDRVNILGFSIFNQSHAFFQEFAQSLNQSWQENCDH
VPFTGPALSSALLFDAVYAVVTAVQELNRSQEIGVKPLSCGSAQIWQHGTSLMNYLRMV
ELEGLTGHIEFNSKGQRSNYALKILQFTRNGFRQIGQWHVAEGLSMDSHLYASNISDTL
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RKPGYFSFLDPFSPGVWLFMLLAYLAVSCVLFLVARLTPYEWYSPHPCAQGRCNLLVNQ
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DVPIESVDDLADQTAIEYGTIHGGSSMTFFQNSRYQTYQRMWNYMYSKQPSVFVKSTEE
GIARVLNSNYAFLLESTMNEYYRQRNCNLTQIGGLLDTKGYGIGMPVGSVFRDEFDLAI
LQLQENNRLEILKRKWWEGGKCPKEEDHRAKGLGMENIGGIFVVLICGLIVAIFMAMLE
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TLSNGKLCGAGEPDQLAQRLAQEAALVARGCTHIRVCPECRRFQGLRARPSPARSEESL
EWEKTTNSSEPE

Figure 12

Cytogenetic Position	Description	Breakpoint YAC Clones	Breakpoint BAC Clones (Acc. No.)
2p12	Inversion breakpoint	915_f_7	-
2q32.1	Inversion breakpoint	941_h_12	RP11-358M9 (AC020595)
2q21.3	Translocation breakpoint	766_c_12	RP11-250H22 (AC011996)
11q23.3	Upper insertion breakpoint	936_d_9	RP11-89P5 (AC009641)
11q24.2	Translocation/Insertion breakpoint	749_d_2	RP11-687M24 (AP001007)

Figure 13

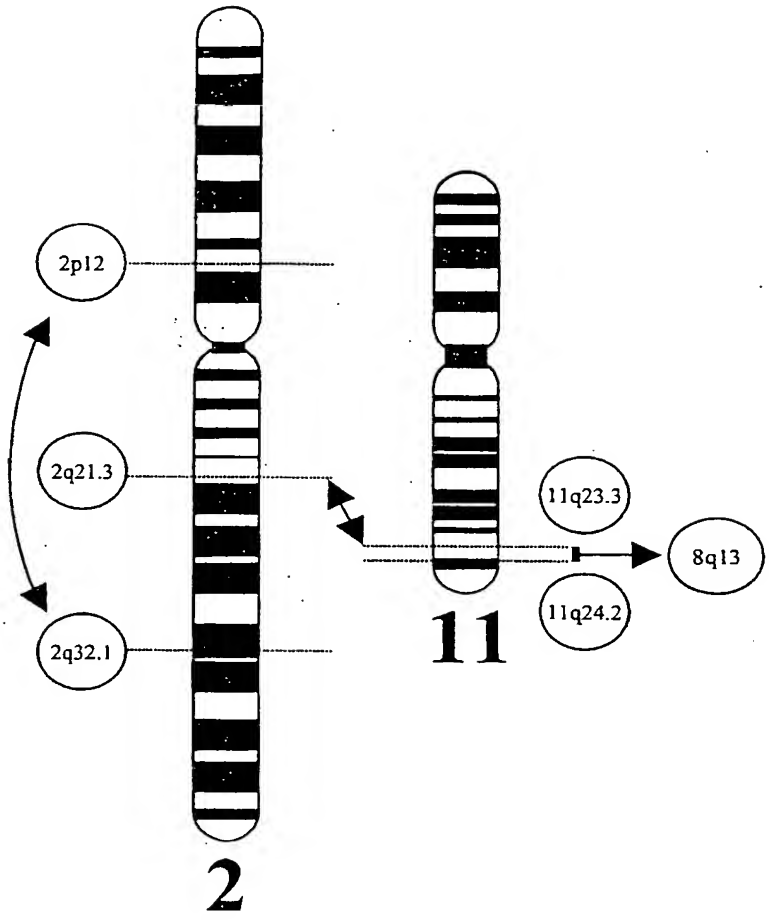
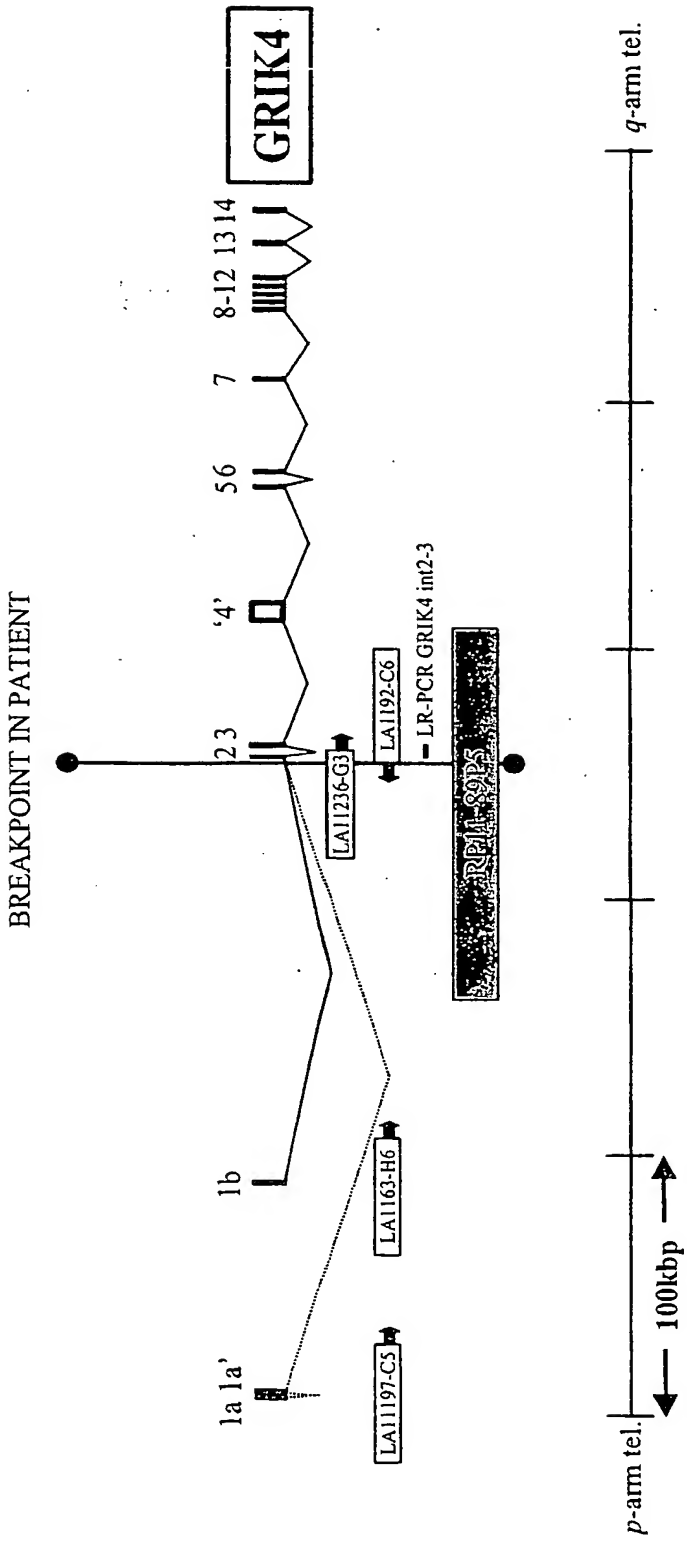


Figure 14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8-12 13 14
7
5 6
'4'
2 3
1b
1a 1a'
BREAKPOINT IN PATIENT
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LA1192-C6
LR-PCR GRIK4 int2-3
LA1163-H6
LA11197-C5
RP11-89P5
q-arm tel.
p-arm tel.
100kbp

Figure 15

Exon 1a

GCGTGGTAGCATGTGCCTGTAATCCCAGTGCTTTGGGACACCGAGGCAGGAGGATCACT
CGAGCCCAGGAGTGCGAGGCTGCAgtgagttatgatcatac

Exon 1a'

agatttgtcttctctgccagGTGACGCTAGACTTCAGGAAGACCCCCCATTTCTGCTCC
ACTCCTGGGCTTGGAGAAGAGTACAGCTGCTCTTGACTGGTGGGACCTTTTGCTGGCTA
GGGGTGATGGGAGAAGCAAGAGAGGGATCCACACACCTGCGCTTAGCTTTCTATGACCT
GGGCGGATGGAGGCCAAAGgtaaggtgggatgaga
M E A K A

Exon 1b

CCATGAGGATTCATAGAAGATGCCCCGCGTCTCGGCGCCTTTGGTGCTGCTTCCTGCGT
M P R V S A P L V L L P A W
GGCTCGTGATGGTCGCCTGCAGCCCGCACTCCTTGAGGATCGgtaagtgtggcccagct
L V M V A C S P H S L R I A

Exon 2

gaaacccccccccagCTGCTATCTTGGACGACCCCATGGAGTGCAGCAGAGGGGAGCGGC
A I L D D P M E C S R G E R L
TCTCCATCACCCTGGCCAAGAACCGCATCAACCGCGCTCCTGAGAGGCTGGGCAAGGCC
S I T L A K N R I N R A P E R L G K A
AAGGTCGAAGTGGACATCTTTGAGCTTCTCAGAGACAGCGAGTACGAGACTGCAGAAAC
K V E V D I F E L L R D S E Y E T A E T

CAgtacgtagactggg
M

Figure 16
Alternative nucleic acid sequence. Exons 1a-1a'-2-etc.

```
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  61 gagcccagga gtgcgaggct gcagtgacgc tagacttcag gaagaccccc catttctgct
 121 ccactcctgg gcttggagaa gagtacagct gctcttgact ggtgggacct tttgctggct
 181 aggggtgatg ggagaagcaa gagagggatc cacacacctg cgcttagctt tctatgacct
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 601 agcaacactg acatcagcgt ggctgtagct gggatcctga acttcttcaa ctgcaccacc
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1201 cagcacggca ccagcctcat gaactacctg cgcatggtag aattggaagg tcttaccggc
1261 cacattgaat tcaacagcaa aggccagagg tccaactacg ctttgaaaat cttacagttc
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1381 agccacctct atgcctccaa catctcggac actctcttca acaccaccct ggtcgtcacc
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2881 gcgcagagac tggcgcagga ggccgccctg gtggcccgcg gctgcacgca catccgcgtc
2941 tgccccgagt gccgccgctt ccagggcctg cgggcacggc cgtcgcccgc ccgcagcgag
3001 gagagcctgg agtgggagaa aaccaccaac agcagcgagc ccgagtag
```

Figure 17

Complete alternative protein sequence

MEAKAAILDDPMECSRGERLSITLAKNRINRAPERLGKAKVEVDIFELLRDSEYETAET
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VQELNRSQEIGVKPLSCGSAQIWQHGTSLMNYLRMVELEGLTGHIEFNSKGQRSNYALK
ILQFTRNGFRQIGQWHVAEGLSMDSHLYASNISDTLFNTTLVVTTILENPYLMLKGNHQ
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LAVAGLTITAEREKVIDFSKPFMTLGISILYRIHMGRKPGYFSFLDPFSPGVWLFMLLA
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RALSTRCVSGVWWAFTLIIISSYTANLAAFLTVQRMDVPIESVDDLADQTAIEYGTIHG
GSSMTFFQNSRYQTYQRMWNYMYSKQPSVFVKSTEEGIARVLNSNYAFLLESTMNEYYR
QRNCNLTQIGGLLDTKGYGIGMPVGSVFRDEFDLAILQLQENNRLEILKRKWWEGGKCP
KEEDHRAKGLGMENIGGIFVVLICGLIVAIFMAMLEFLWTLRHSEATEVSVCQEMVTEL
RSIILCQDSIHPRRRRAAVPPPRPPIPEERRPRGTATLSNGKLCGAGEPDQLAQRLAQE
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Figure 18

NPAS3 (NM_022123) nucleic acid sequence (spliceform 1b-3-4etc)

```
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  61 aaaaatagca ggaagatggc gcccaccaag cccagctttc agcaggatcc ttccaggcga
 121 gaacgtttac aagcattgag aaaggagaaa tcccgagatg ctgctcgctc ccgccgggga
 181 aaagaaaact ttgagttcta tgaattggcc aagttgttgc ctcttcctgc agccattacc
 241 agccagctcg acaaggcatc catcattcga cttacaatta gctatctgaa aatgagggac
 301 tttgctaacc agggggaccc tccgtggaac ttgcgaatgg aaggccctcc acctaacaca
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 421 gcacatttgg gaagccacat tttgcagtcc ctggatggct ttgtatttgc actaaatcag
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 541 gagctgacag gcagcagtgt ctttgactat gtccaccccg gagatcacgt ggagatggct
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 781 aaatctactc tgaccaaacg cggtgtgcac atcaaatcat caggatataa ggtgattcac
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 961 attgactgcc atatgttcgt cactcgagta aatatggacc tcaatatcat ttactgtgaa
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1741 gaggcgggcg cgcaggcctc cagcaagcac cagaagcgca agaaaaggcg gaaacggcaa
1801 aagggcggca gcgccagccg ccggcgcctg tccagcgcgt cgagcccagg cggcctggac
1861 gcgggcctgg tggagccccc gcggctgctg tcctcccccа acagtgcctc ggtgctcaag
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1981 ccgcccaacc gggagatctc caggaacgag tccccctaca gcatgaccaa gccccccagc
2041 tctgagcact tcccgtcccc gcagggcggc ggcggtgggg gtggcggtgg cgggggggctg
2101 cacgtggcca ttcccgactc ggtcctcacc ccgcccggcg ccgacggcgc ggccgcccgc
2161 aagactcagt tcggcgcctc ggccaccgcg gccctggccc ccgtcgcctc cgacccgctg
2221 tcacccccgc tctcggcgtc cccgcgggac aagcaccccg ggaacggcgg cgggggcggg
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2461 accatccgct acgcgcccgc cgaggtgacc ctggccatgc agagcaacct gctgcccaac
2521 gcgcacgctg ttaacttcgt ggacgttaac agccccggct ttggcctcga ccccaagacg
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2641 gcagtgagcg cagctagcct gacgcagatg cccgccggca acgtgttcac cacggccgag
2701 ggactcttct ccacgctgcc cttccccgtc tacagcaacg gcatccacgc ggcacagact
2761 ctggagcgca aggaggactg aggcgccgcc cgtcctgggc ccggccaggc cccgcttgga
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3001 tgccgttttg tcttcttcta aggtgtgtgt tgggttgttt tgctttcctt tgcatcttta
3061 ttaagatgtc tttcatgtgt atatgcctct gccatagaat actcagtctt gtggtcaaga
3121 gagttctcaa gtgacaacca ttggggtttc ttcataaaga tcttgatatg atcaagatgg
3181 aaagagacaa gcataaacaa tgtgccctgt ttgactaagt caaatgaaat agggtggttt
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3301 gaatttaatt ctctttttac ggttaagatt ttaagatttt cttacttgca cataaaaata
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3421 cctcgtgc
```

Figure 19

NPAS3 protein sequence (spliceform 1b-3-4etc.)

MAPTKPSFQQDPSRRERLQALRKEKSRDAARSRRGKENFEFYELAKLLPLPAAITSQLD
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GSHILQSLDGFVFALNQEGKFLYISETVSIYLGLSQVELTGSSVFDYVHPGDHVEMAEQ
LGMKLPPGRGLLSQGTAEDGASSASSSSQSETPEPVESTSPSLLTTDNTLERSFFIRMK
STLTKRGVHIKSSGYKVIHITGRLRLRVSLSHGRTVPSQIMGLVVVAHALPPPTINEVR
IDCHMFVTRVNMDLNIIYCENRISDYMDLTPVDIVGKRCYHFIHAEDVEGIRHSHLDLL
NKGQCVTKYYRWMQKNGGYIWIQSSATIAINAKNANEKNIIWVNYLLSNPEYKDTPMDI
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PGGLDAGLVEPPRLLSSPNSASVLKIKTEISEPINFDNDSSIWNYPPNREISRNESPYS
MTKPPSSEHFPSPQGGGGGGGGGGGLHVAIPDSVLTPPGADGAAARKTQFGASATAALA
PVASDPLSPPLSASPRDKHPGNGGGGGGGGGAGGGGPSASNSLLYTGDLEALQRLQAG
NVVLPLVHRVTGTLAATSTAAQRVYTTGTIRYAPAEVTLAMQSNLLPNAHAVNFVDVNS
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YSNGIHAAQTLERKED
```
```

Figure 20

NPAS3 nucleic acid sequence (spliceform incorporating exons 1a-2-3-4etc) similar to mouse cDNA with accession number NM_013780)

```
   1 ATGGGGAGGG CCGGCGCCGC GGCCAACGGC ACCCCGCAGA ACGTCCAGGG CATCACCTCC
  61 TACCAGCAGC GAATAACTGC CCAGCATCCT CTGCCCAACC AATCAGAATG TAGGAAAATC
 121 TACAGATATG ACGGAATCTA CTGTGAATCT ACCTACCAGA ATTTACAAGC ATTGAGAAAG
 181 GAGAAATCCC GAGATGCTGC TCGCTCCCGC CGGGGAAAAG AAAACTTTGA GTTCTATGAA
 241 TTGGCCAAGT TGTTGCCTCT TCCTGCAGCC ATTACCAGCC AGCTCGACAA GGCATCCATC
 301 ATTCGACTTA CAATTAGCTA TCTGAAAATG AGGGACTTTG CTAACCAGGG GGACCCTCCG
 361 TGGAACTTGC GAATGGAAGG CCCTCCACCT AACACATCAG TAAAAGGTGC ACAGCGAAGG
 421 AGAAGCCCCA GTGCACTAGC CATTGAAGTA TTTGAAGCAC ATTTGGGAAG CCACATTTTG
 481 CAGTCCCTGG ATGGCTTTGT ATTTGCACTA AATCAGGAAG GAAAATTTTT GTACATTTCC
 541 GAAACAGTCT CCATCTACCT AGGCCTCTCA CAAGTGGAGC TGACAGGCAG CAGTGTCTTT
 601 GACTATGTCC ACCCCGGAGA TCACGTGGAG ATGGCTGAGC AGCTGGGCAT GAAGCTCCCC
 661 CCTGGGCGGG GTCTCCTGTC ACAGGGCACT GCTGAGGACG GAGCCAGCTC AGCATCTTCC
 721 TCCTCTCAGT CGGAGACCCC CGAGCCAGTG GAGTCAACCA GCCCCAGTCT GCTAACCACT
 781 GACAACACTC TTGAGCGTTC CTTTTTCATC CGAATGAAAT CTACTCTGAC CAAACGCGGT
 841 GTGCACATCA AATCATCAGG ATATAAGGTG ATTCACATAA CAGGCCGGCT ACGCCTGAGA
 901 GTGTCGCTGT CCCACGGGAG GACCGTCCCC AGCCAAATCA TGGGTCTCGT GGTTGTTGCG
 961 CATGCCTTGC CTCCCCCTAC GATCAATGAA GTCAGAATTG ACTGCCATAT GTTCGTCACT
1021 CGAGTAAATA TGGACCTCAA TATCATTTAC TGTGAAAATA GGATTAGTGA TTATATGGAT
1081 CTGACCCCTG TAGATATCGT AGGGAAGAGA TGCTACCACT TCATCCATGC TGAAGACGTG
1141 GAGGGCATCA GGCACAGTCA CTTGGACTTG CTGAATAAGG GTCAGTGTGT GACAAAGTAC
1201 TATCGCTGGA TGCAGAAGAA CGGAGGATAT ATTTGGATAC AGTCCAGTGC CACCATAGCT
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1381 TCCGAATCCT CGGAGACATC CGACTCTGAG TCAGACTCTA AAGACACCTC AGGTATTACA
1441 GAGGACAACG AGAACTCCAA GTCCGACGAG AAGGGGAACC AGTCCGAGAA CAGCGAAGAC
1501 CCGGAGCCCG ACCGGAAGAA GTCGGGCAAC GCGTGTGACA ACGACATGAA CTGCAACGAC
1561 GACGGCCACA GCTCCAGTAA CCCGGACAGC CGCGACAGCG ACGACAGCTT CGAGCACTCG
1621 GACTTTGAGA ACCCCAAGGC GGGCGAGGAC GGCTTCGGTG CTCTGGGCGC GATGCAGATC
1681 AAGGTGGAGC GCTACGTGGA GAGCGAGTCG GACCTGCGGC TGCAGAACTG CGAGTCACTC
1741 ACGTCCGACA GCGCCAAGGA CTCGGACAGC GCAGGCGAGG CGGGCGCGCA GGCCTCCAGC
1801 AAGCACCAGA AGCGCAAGAA AAGGCGGAAA CGGCAAAAGG GCGGCAGCGC CAGCCGCCGG
1861 CGCCTGTCCA GCGCGTCGAG CCCAGGCGGC CTGGACGCGG GCCTGGTGGA GCCCCCGCGG
1921 CTGCTGTCCT CCCCCAACAG TGCCTCGGTG CTCAAGATCA AGACGGAGAT CTCAGAACCC
1981 ATCAATTTCG ACAATGACAG CAGCATCTGG AACTACCCGC CCAACCGGGA GATCTCCAGG
2041 AACGAGTCCC CCTACAGCAT GACCAAGCCC CCCAGCTCTG AGCACTTCCC GTCCCCGCAG
2101 GGCGGCGGCG GTGGGGGTGG CGGTGGCGGG GGGCTGCACG TGGCCATTCC CGACTCGGTC
2161 CTCACCCCGC CCGGCGCCGA CGGCGCGGCC GCCCGCAAGA CTCAGTTCGG CGCCTCGGCC
2221 ACCGCGGCCC TGGCCCCCGT CGCCTCCGAC CCGCTGTCAC CCCCGCTCTC GGCGTCCCCG
2281 CGGGACAAGC ACCCCGGGAA CGGCGGCGGG GGCGGGGGCG GGGGCGGCGG CGCGGGGGGC
2341 GGCGGCCCCA GCGCGTCCAA CTCCTTGCTG TACACTGGGG ACCTGGAGGC GCTGCAGAGG
2401 TTGCAGGCGG GCAACGTCGT GCTCCCGCTG GTGCACAGGG TGACCGGGAC CCTGGCCGCC
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2521 GTGACCCTGG CCATGCAGAG CAACCTGCTG CCCAACGCGC ACGCTGTTAA CTTCGTGGAC
2581 GTTAACAGCC CCGGCTTTGG CCTCGACCCC AAGACGCCCA TGGAGATGCT CTACCACCAC
2641 GTGCACCGGC TCAACATGTC AGGACCGTTC GGCGGCGCAG TGAGCGCAGC TAGCCTGACG
2701 CAGATGCCCG CCGGCAACGT GTTCACCACG GCCGAGGGAC TCTTCTCCAC GCTGCCCTTC
2761 CCCGTCTACA GCAACGGCAT CCACGCGGCA CAGACTCTGG AGCGCAAGGA GGACTGAGGC
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```

2881 TAGACCTTTA ATTCTAGCAC TTTGAATTCG AGCAGGTCAG CGTCTTCTCT CGCCACGACG
2941 GTCCCCATTC CACCCCCTCT T

Figure 21

NPAS3 protein sequence of spliceform incorporating exons 1a-2-3-4etc.

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PPWNLRMEGPPPNTSVKGAQRRRSPSALAIEVFEAHLGSHILQSLDGFVFALNQEGKFL
YISETVSIYLGLSQVELTGSSVFDYVHPGDHVEMAEQLGMKLPPGRGLLSQGTAEDGAS
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DSDDSFEHSDFENPKAGEDGFGALGAMQIKVERYVESESDLRLQNCESLTSDSAKDSDS
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VLKIKTEISEPINFDNDSSIWNYPPNREISRNESPYSMTKPPSSEHFPSPQGGGGGGGG
GGGLHVAIPDSVLTPPGADGAAARKTQFGASATAALAPVASDPLSPPLSASPRDKHPGN
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RVYTTGTIRYAPAEVTLAMQSNLLPNAHAVNFVDVNSPGFGLDPKTPMEMLYHHVHRLN
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Figure 22

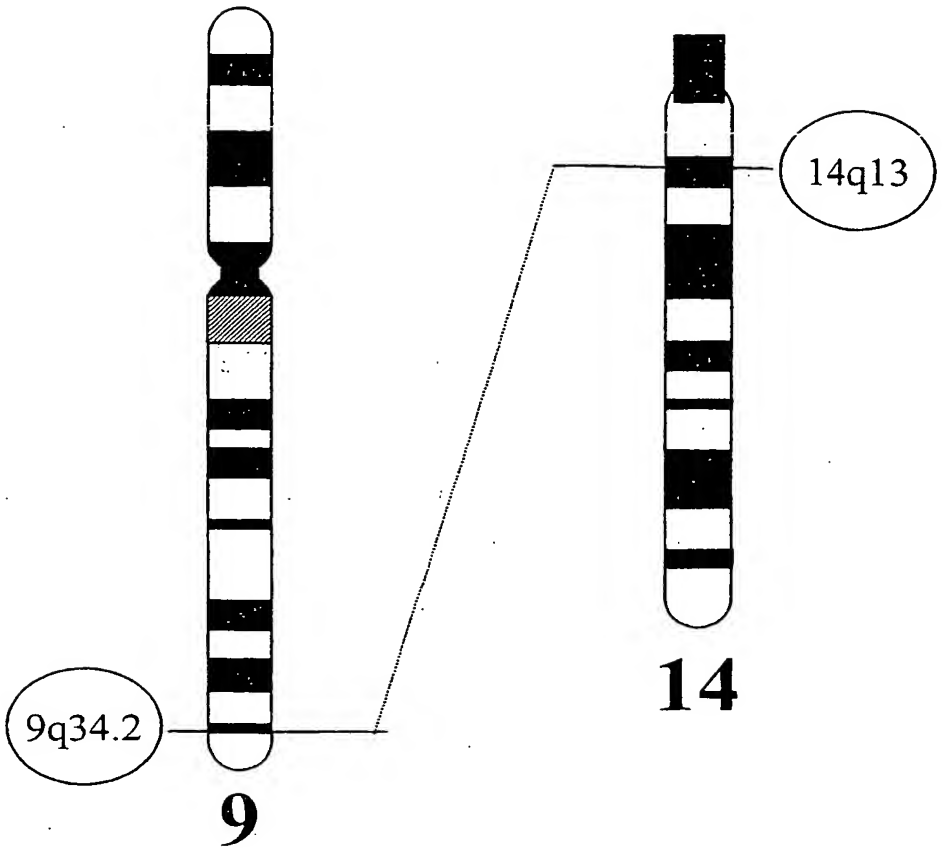
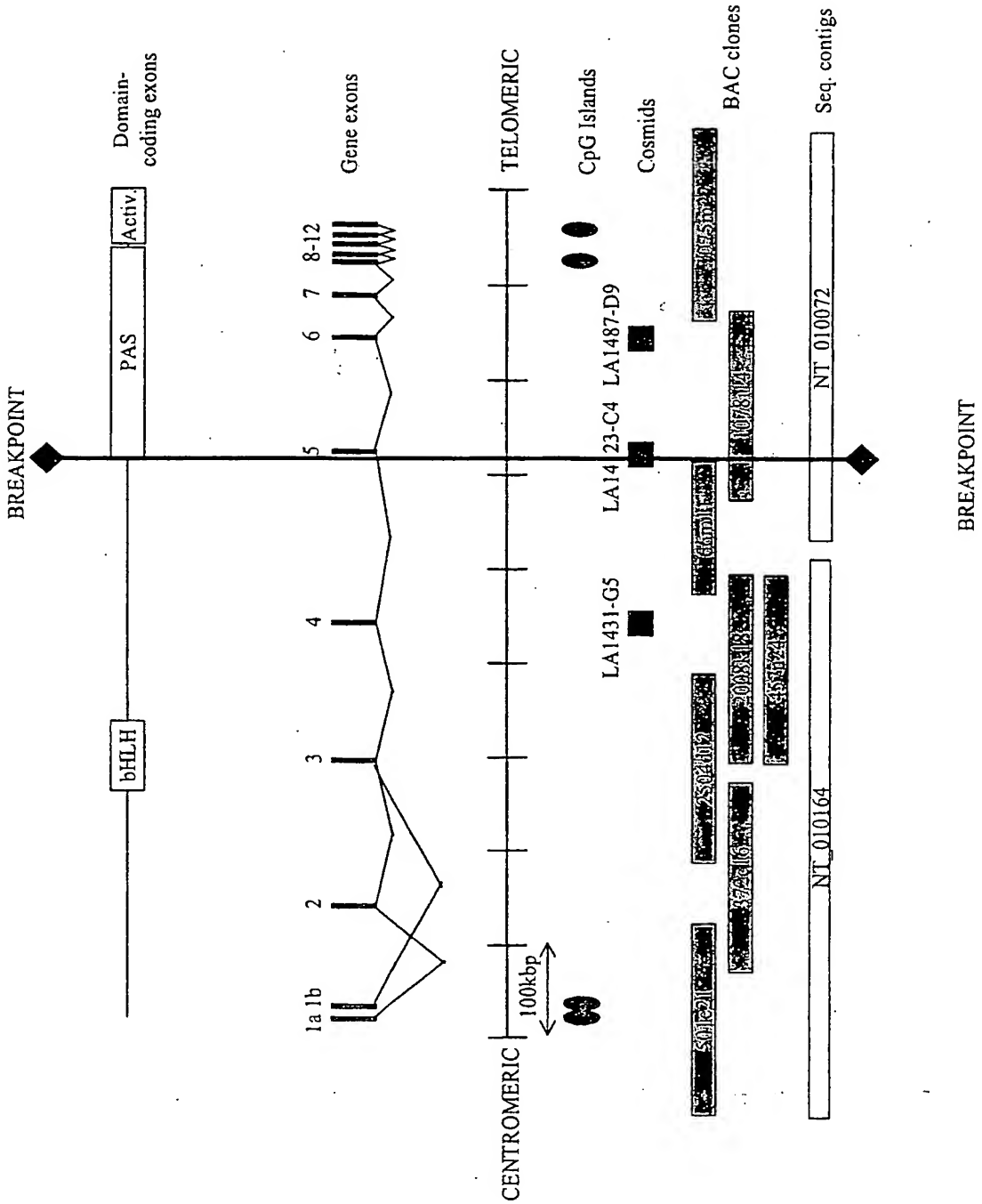


Figure 23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bHLH
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2
3
4
5
6
7
8-12
Gene exons
CENTROMERIC
100kbp
TELOMERIC
LA1431-G5
LA14 23-C4
LA1487-D9
CpG Islands
Cosmids
BAC clones
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NT_010072
Seq. contigs
BREAKPOINT

Figure 24

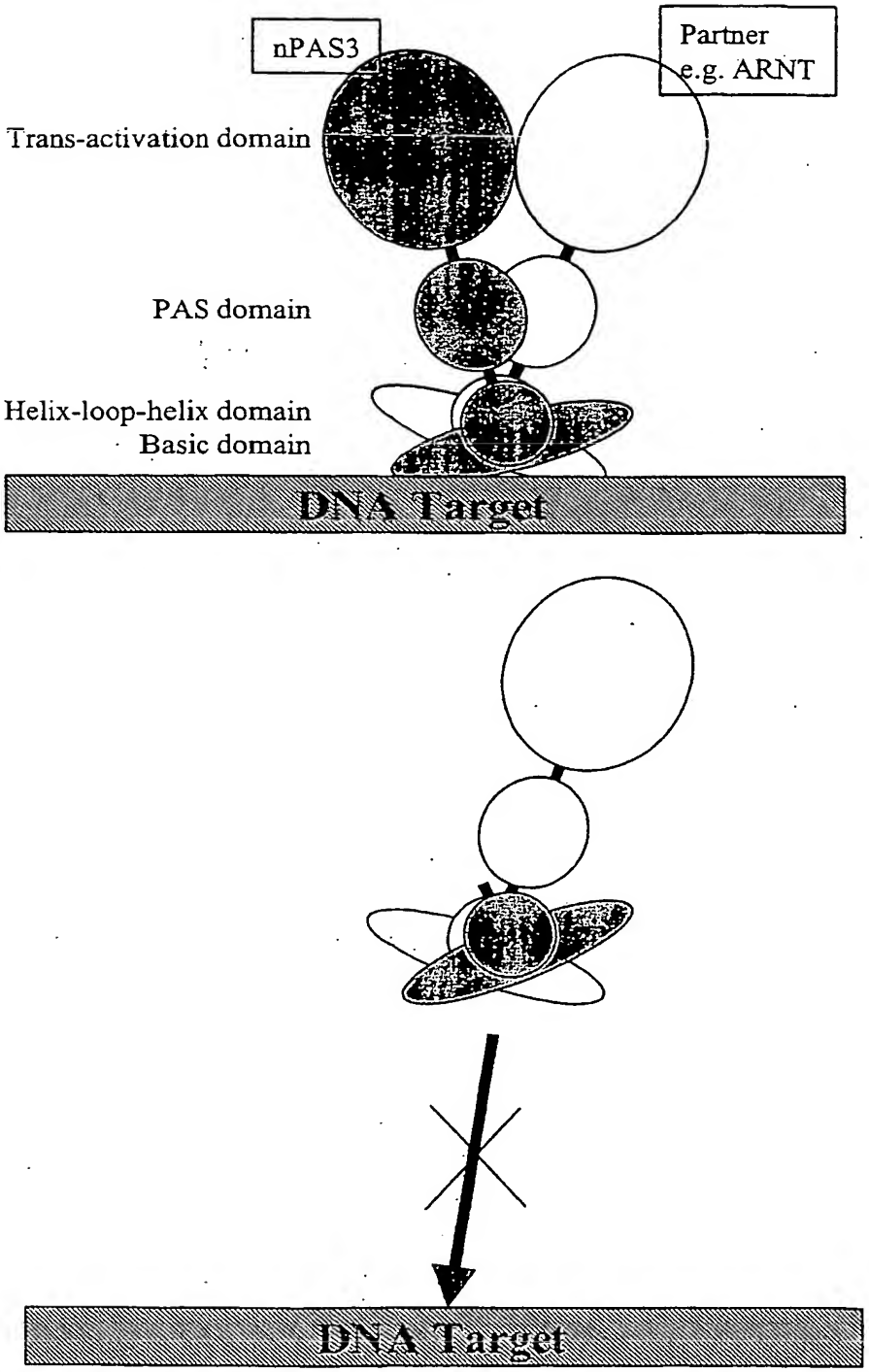
nPAS3
Partner
e.g. ARNT
Trans-activation domain
PAS domain
Helix-loop-helix domain
Basic domain
DNA Target
DNA Target

Figure 25

PDE4B1 (acc. L20966) Nucleic acid sequence

```
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 121 atattttcca cctctataat gaagaaaagc aggagtgtga tgacggtgat ggctgatgat
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 601 cttccaagcg agcaacacgg cgatgacttg attgtaactc cttttgccca ggtccttgcc
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3061 gctgtaaaca gaataaaatt gaacaaatta gggggtagaa aggagcagtg gtgtcgttca
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3181 ggccgc

Figure 26

PDE4B1 Protein sequence

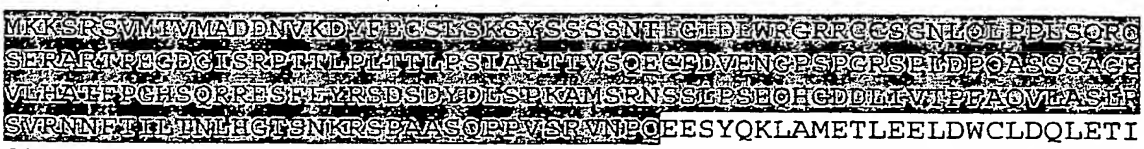

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Figure 27

PDE4B3 (acc. U85048) Nucleic acid sequence

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 421 ccaagcgagc aacacggcga tgacttgatt gtaactcctt ttgcccaggt ccttgccagc
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1201 cagtcgaccc atgttctcct ttctacacca gcattagacg ctgtcttcac agatttggag
1261 atcctggctg ccatttttgc agctgccatc catgacgttg atcatcctgg agtctccaat
1321 cagtttctca tcaacacaaa ttcagaactt gctttgatgt ataatgatga atctgtgttg
1381 gaaaatcatc accttgctgt gggtttcaaa ctgctgcaag aagaacactg tgacatcttc
1441 atgaatctca ccaagaagca gcgtcagaca ctcaggaaga tggttattga catggtgtta
1501 gcaactgata tgtctaaaca tatgagcctg ctggcagacc tgaagacaat ggtagaaacg
1561 aagaaagtta caagttcagg cgttcttctc ctagacaact ataccgatcg cattcaggtc
1621 cttcgcaaca tggtacactg tgcagacctg agcaacccca ccaagtcctt ggaattgtat
1681 cggcaatgga cagaccgcat catggaggaa tttttccagc agggagacaa agagcgggag
1741 aggggaatgg aaattagccc aatgtgtgat aaacacacag cttctgtgga aaaatcccag
1801 gttggtttca tcgactacat tgtccatcca ttgtgggaga catgggcaga tttggtacag
1861 cctgatgctc aggacattct cgatacctta gaagataaca ggaactggta tcagagcatg
1921 atacctcaaa gtccctcacc accactggac gagcagaaca gggactgcca gggtctgatg
1981 gagaagtttc agtttgaact gactctcgat gaggaagatt ctgaaggacc tgagaaggag
2041 ggagagggac acagctattt cagcagcaca aagacgcttt gtgtgattga tccagaaaac
2101 agagattccc tgggagagac tgacatagac attgcaacag aagacaagtc ccccgtggat
2161 aca
```

Figure 28

PDE4B3 Protein sequence

EESYQKLAMETLEELDWCLDQLETIQTYRSVSEMASNKFK
RMLNRELTHLSEMSRSGNQVSEYISNTFLDKQNDVEIPSPTQKDREKKKKQQLMTQISG
VKKLMHSSSLNNTSISRFGVNTENEDHLAKELEDLNKWGLNIFNVAGYSHNRPLTCIMY
AIFQERDLLKTFRISSDTFITYMMTLEDHYHSDVAYHNSLHAADVAQSTHVLLSTPALD
AVFTDLEILAAIFAAAIHDVDHPGVSNQFLINTNSELALMYNDESVLENHHLAVGFKLL
QEEHCDIFMNLTKKQRQTLRKMVIDMVLATDMSKHMSLLADLKTMVETKKVTSSGVLLL
DNYTDRIQVLRNMVHCADLSNPTKSLELYRQWTDRIMEEFFQQGDKERERGMEISPMCD
KHTASVEKSQVGFIDYIVHPLWETWADLVQPDAQDILDTLEDNRNWYQSMIPQSPSPPL
DEQNRDCQGLMEKFQFELTLDEEDSEGPEKEGEGHSYFSSTKTLCVIDPENRDSLGETD
IDIATEDKSPVDT

Figure 29

PDE4B2 (acc. NM_002600) Nucleic acid seqeunce

```
   1 gaattcctcc tctcttcacc ccgttagctg ttttcaatgt aatgctgccg tccttctctt
  61 gcactgcctt ctgcgctaac acctccattc ctgtttataa ccgtgtattt attacttaat
 121 gtatataatg taatgttttg taagttatta atttatatat ctaacattgc ctgccaatgg
 181 tggtgttaaa tttgtgtaga aaactctgcc taagagttac gacttttttct tgtaatgttt
 241 tgtattgtgt attatataac ccaaacgtca cttagtagag acatatggcc cccttggcag
 301 agaggacagg ggtgggcttt tgttcaaagg gtctgccctt tccctgcctg agttgctact
 361 tctgcacaac ccctttatga accagttttc acccgaattt tgactgtttc atttagaaga
 421 aaagcaaaat gagaaaaagc tttcctcatt tctccttgag atggcaaagc actcagaaat
 481 gacatcacat accctaaaga accctgggat gactaaggca gagagagtct gagaaaactc
 541 tttggtgctt ctgcctttag ttttaggaca catttatgca gatgagctta taagagaccg
 601 ttcccctccgc cttcttcctc agaggaagtt tcttggtaga tcaccgacac ctcatccagg
 661 cgggggggttg gggggaaact tggcaccagc catcccaggc agagcaccac tgtgatttgt
 721 tctcctggtg gagagagctg gaaggaagga gccagcgtgc aaataatgaa ggagcacggg
 781 ggcaccttca gtagcaccgg aatcagcggt ggtagcggtg actctgctat ggacagcctg
 841 cagccgctcc agcctaacta catgcctgtg tgtttgtttg cagaagaatc ttatcaaaaa
 901 ttagcaatgg aaacgctgga ggaattagac tggtgtttag accagctaga gaccatacag
 961 acctaccggt ctgtcagtga gatggcttct aacaagttca aaagaatgct gaaccgggag
1021 ctgacacacc tctcagagat gagccgatca gggaaccagg tgtctgaata catttcaaat
1081 actttcttag acaagcagaa tgatgtggag atcccatctc ctacccagaa agacagggag
1141 aaaaagaaaa agcagcagct catgacccag ataagtggag tgaagaaatt aatgcatagt
1201 tcaagcctaa acaatacaag catctcacgc tttggagtca acactgaaaa tgaagatcac
1261 ctggccaagg agctggaaga cctgaacaaa tggggtctta acatctttaa tgtggctgga
1321 tattctcaca atagacccct aacatgcatc atgtatgcta tattccagga aagagacctc
1381 ctaaagacat tcagaatctc atctgacaca tttataacct acatgatgac tttagaagac
1441 cattaccatt ctgacgtggc atatcacaac agcctgcacg ctgctgatgt agcccagtcg
1501 acccatgttc tcctttctac accagcatta gacgctgtct tcacagattt ggagatcctg
1561 gctgccattt ttgcagctgc catccatgac gttgatcatc ctggagtctc caatcagttt
1621 ctcatcaaca caaattcaga acttgctttg atgtataatg atgaatctgt gttggaaaat
1681 catcaccttg ctgtgggttt caaactgctg caagaagaac actgtgacat cttcatgaat
1741 ctcaccaaga agcagcgtca gacactcagg aagatggtta ttgacatggt gttagcaact
1801 gatatgtcta aacatatgag cctgctggca gacctgaaga caatggtaga aacgaagaaa
1861 gttacaagtt caggcgttct tctcctagac aactataccg atcgcattca ggtccttcgc
1921 aacatggtac actgtgcaga cctgagcaac cccaccaagt ccttggaatt gtatcggcaa
1981 tggacagacc gcatcatgga ggaatttttc cagcagggag acaaagagcg ggagagggga
2041 atggaaatta gcccaatgtg tgataaacac acagcttctg tggaaaaatc ccaggttggt
2101 ttcatcgact acattgtcca tccattgtgg gagacatggg cagatttggt acagcctgat
2161 gctcaggaca ttctcgatac cttagaagat aacaggaact ggtatcagag catgatacct
2221 caaagtccct caccaccact ggacgagcag aacagggact gccagggtct gatggagaag
2281 tttcagtttg aactgactct cgatgaggaa gattctgaag gacctgagaa ggagggagag
2341 ggacacagct atttcagcag cacaaagacg ctttgtgtga ttgatccaga aaacagagat
2401 tccctgggag agactgacat agacattgca acagaagaca agtcccccgt ggatacataa
2461 tccccctctc cctgtggaga tgaacattct atccttgatg agcatgccag ctatgtggta
2521 gggccagccc accatggggg ccaagacctg cacaggacaa gggccacctg gcctttcagt
2581 tacttgagtt tggagtcaga aagcaagacc aggaagcaaa tagcagctca ggaaatccca
2641 cggttgactt gccttgatgg caagcttggt ggagagggct gaagctgttg ctgggggccg
2701 attctgatca agacacatgg cttgaaaatg gaagacacaa aactgagaga tcattctgca
2761 ctaagtttcg ggaacttatc cccgacagtg actgaactca ctgactaata acttcattta
2821 tgaatctttct cacttgtccc tttgtctgcc aacctgtgtg ccttttttgt aaaacatttt
2881 catgtcttta aaatgcctgt tgaatacctg gagtttagta tcaacttcta cacagataag
2941 ctttcaaagt tgacaaactt ttttgactct ttctggaaaa gggaaagaaa atagtcttcc
```

```
3001 ttctttcttg ggcaatatcc ttcactttac tacagttact tttgcaaaca gacagaaagg
3061 atacacttct aaccacattt tacttccttc ccctgttgtc cagtccaact ccacagtcac
3121 tcttaaaact tctctctgtt tgcctgcctc caacagtact tttaactttt tgctgtaaac
3181 agaataaaat tgaacaaatt agggggtaga aaggagcagt ggtgtcgttc accgtgagag
3241 tctgcataga actcagcagt gtgccctgct gtgtcttgga ccctgccccc cacaggagtt
3301 gctacagtcc ctggccctgc ttcccatcct cctctcttca ccccgttagc tgttttcaat
3361 gtaatgctgc cgtccttctc ttgcactgcc ttctgcgcta acacctccat tcctgtttat
3421 aaccgtgtat ttattactta atgtatataa tgtaatgttt tgtaagttat taatttatat
3481 atctaacatt gcctgccaat ggtggtgtta aatttgtgta gaaaactctg cctaagagtt
3541 acgacttttt cttgtaatgt tttgtattgt gtattatata acccaaacgt cacttagtag
3601 agacatatgg ccccccttggc agagaggaca ggggtgggct tttgttcaaa gggtctgccc
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3721 attctcacat tagatactaa atggtttata ctgagtcttt tacttttgta tagcttgata
3781 ggggcagggg caatgggatg tagtttttac ccaggttcta tccaaatcta tgtgggcatg
3841 agttgggtta taactggatc ctactatcat tgtggctttg gttcaaaagg aaacactaca
3901 tttgctcaca gatgattctt ctgattcttc tgaatgctcc cgaactactg actttgaaga
3961 ggtagcctcc tgcctgccat taagcaggaa tgtcatgttc cagttcatta caaaagaaaa
4021 caataaaaca atgtgaattt ttataataaa aaaaaaaaaa aggaattc
```

Figure 30

PDE4B2 Protein sequence

```
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PTQKDREKKKKQQLMTQISGVKKLMHSSSLNNTSISRFGVNTENEDHLAKELEDLNKWG
LNIFNVAGYSHNRPLTCIMYAIFQERDLLKTFRISSDTFITYMMTLEDHYHSDVAYHNS
LHAADVAQSTHVLLSTPALDAVFTDLEILAAIFAAAIHDVDHPGVSNQFLINTNSELAL
MYNDESVLENHHLAVGFKLLQEEHCDIFMNLTKKQRQTLRKMVIDMVLATDMSKHMSLL
ADLKTMVETKKVTSSGVLLLDNYTDRIQVLRNMVHCADLSNPTKSLELYRQWTDRIMEE
FFQQGDKERERGMEISPMCDKHTASVEKSQVGFIDYIVHPLWETWADLVQPDAQDILDT
LEDNRNWYQSMIPQSPSPPLDEQNRDCQGLMEKFQFELTLDEEDSEGPEKEGEGHSYFS
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Figure 31

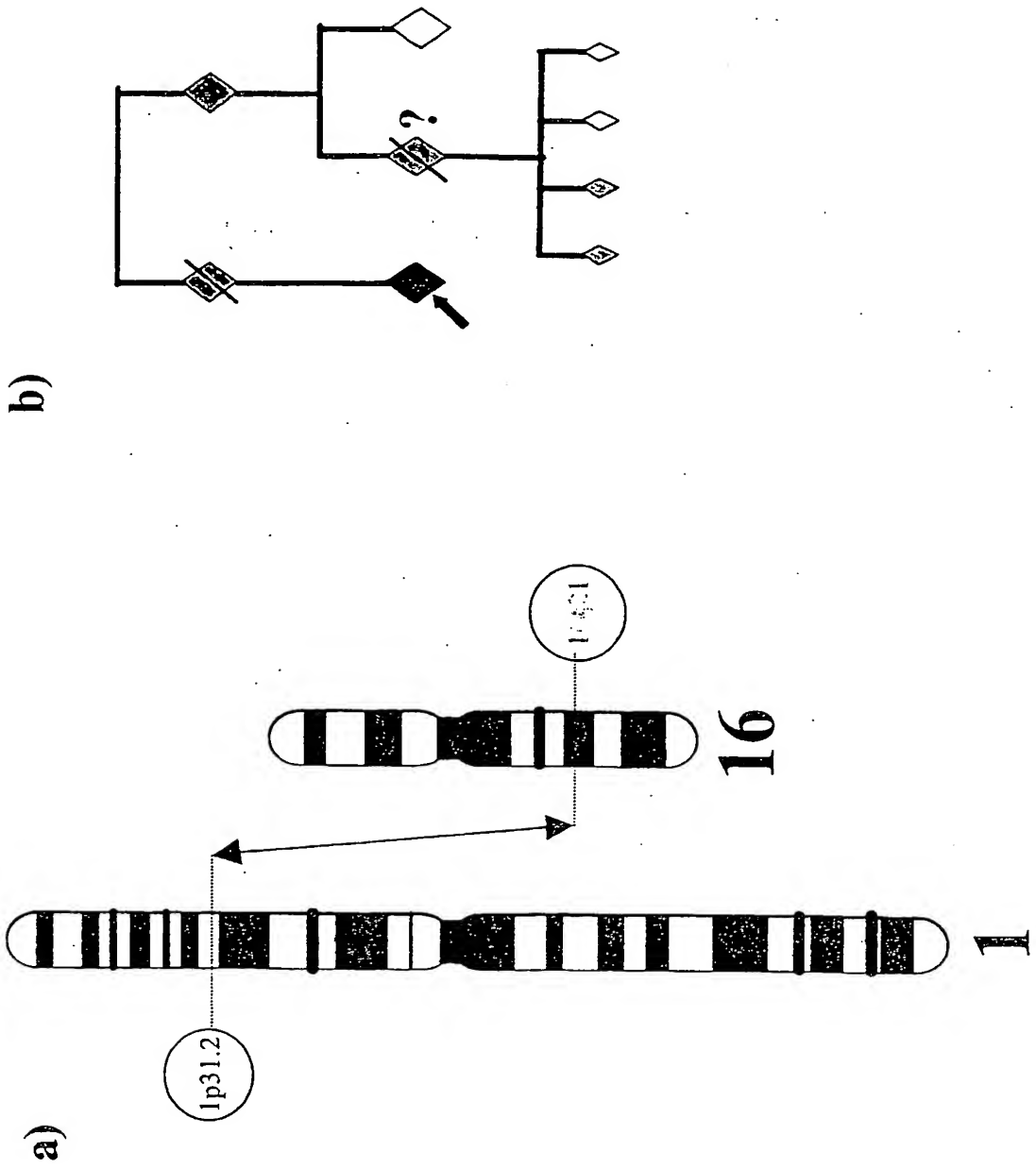

Figure 32

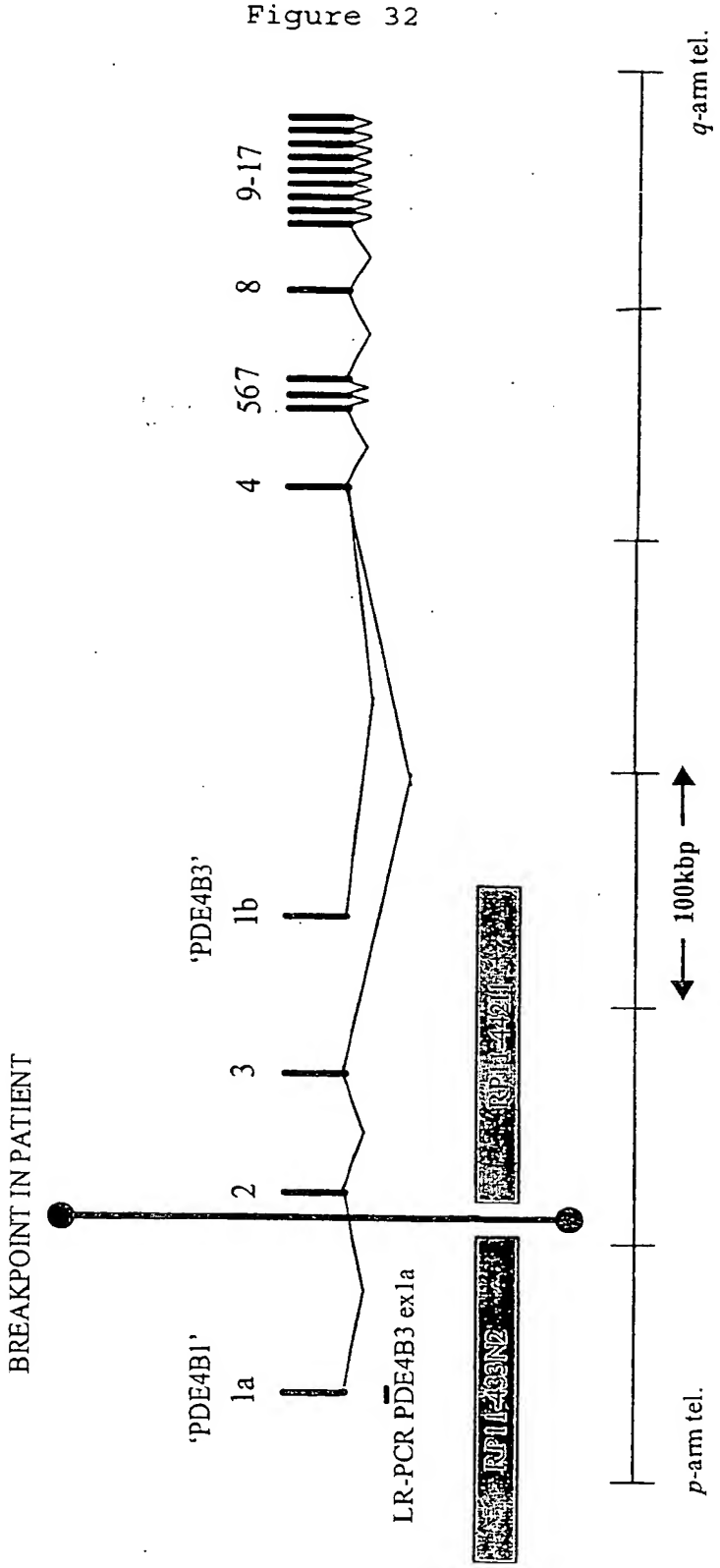
BREAKPOINT IN PATIENT
'PDE4B1'
1a
2
3
'PDE4B3'
1b
4
567
8
9-17
LR-PCR PDE4B3 ex1a
RP11-421F4
RP11-463N2
100kbp
q-arm tel.
p-arm tel.

Figure 33

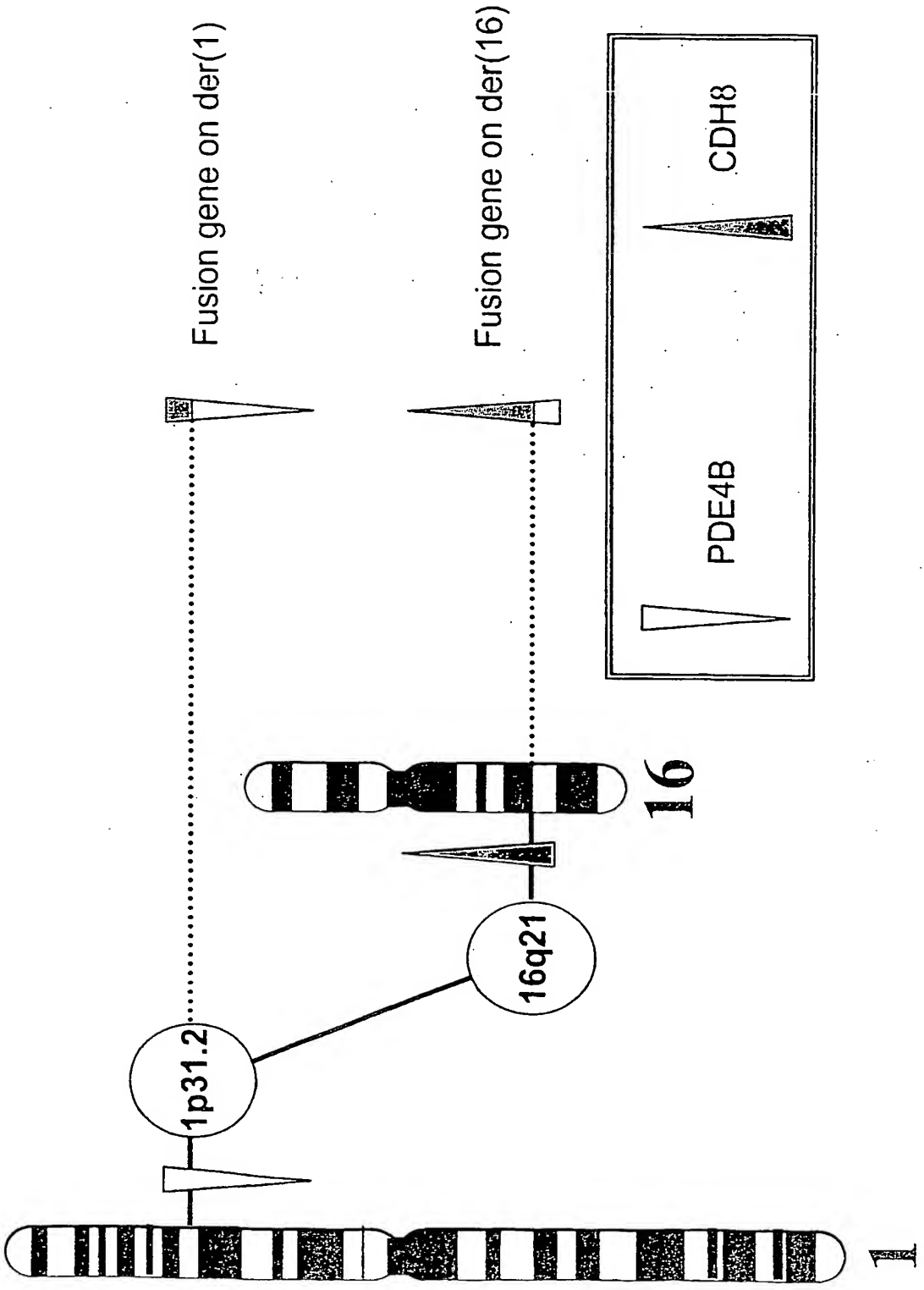
Fusion gene on der(1)
Fusion gene on der(16)
CDH8
PDE4B
16
16q21
1p31.2
1

Figure 34

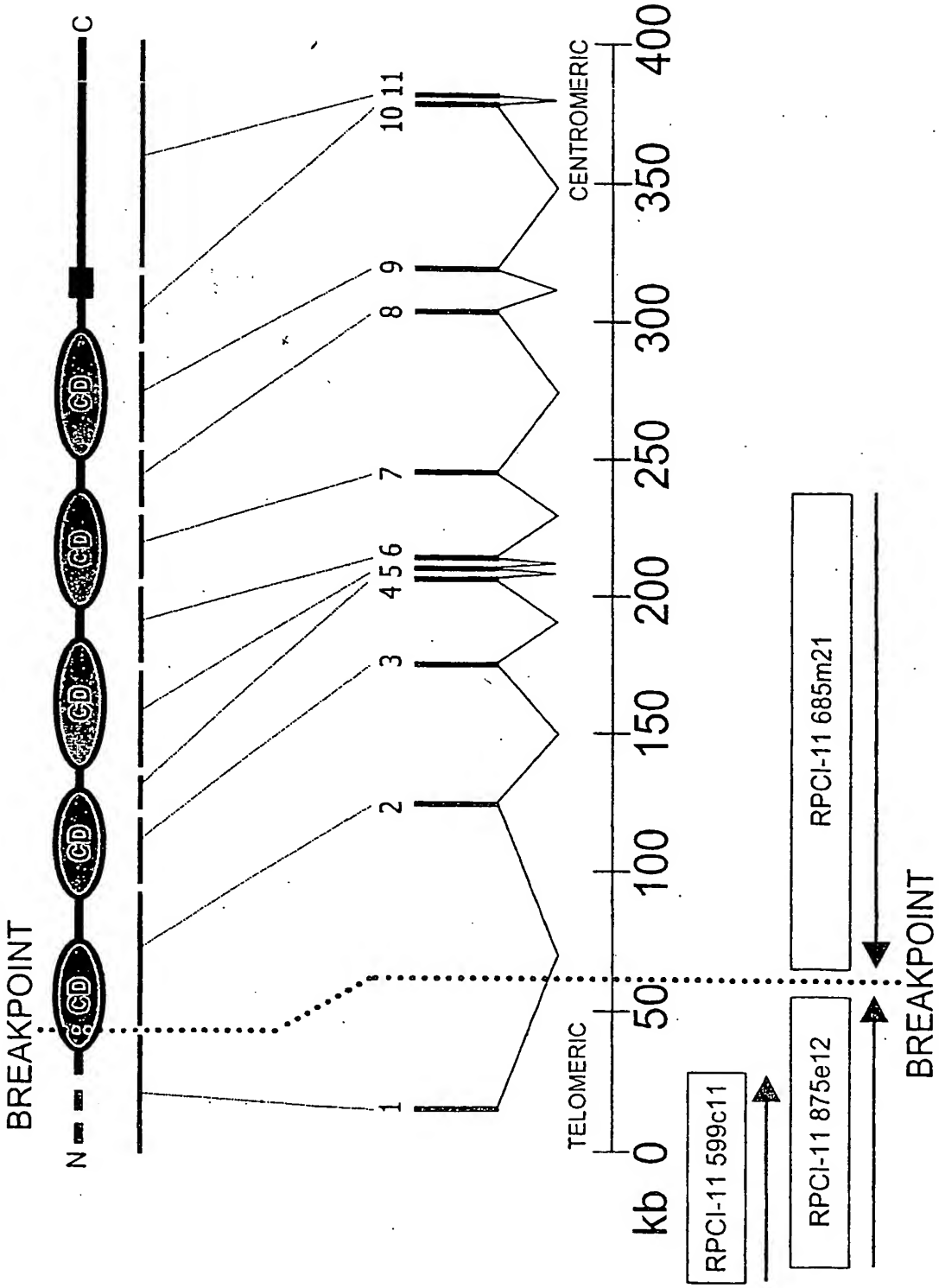
C
N
CD
CD
CD
CD
CD
BREAKPOINT
1
2
3
4 5 6
7
8
9
10 11
CENTROMERIC
TELOMERIC
kb 0
50
100
150
200
250
300
350
400
RPCI-11 599c11
RPCI-11 875e12
RPCI-11 685m21
BREAKPOINT

Figure 35

```
   1 agccatttgt gaacctggag gcttgacatt cgccagcgca gggccccaca agagaaattt
  61 caatgaaaag aaaagccaat ggattgtggt cttagaaaag ctgcttagat gatgtctgtt
 121 tcccgtgcta tagacacgtg gcagagctgt aagtaaatgc tcggcactgc atgatgaatt
 181 ggatggctgc agaccggaga caaaaaaaat aattgtctca ttttcgtggt gatttgctta
 241 actggtggga ccatgccaga acggctagcg gaaatgctct tggatctctg gactccatta
 301 ataatattat ggattactct tccccttgc atttacatgg ctccgatgaa tcagtctcaa
 361 gttttaatga gtggatcccc tttggaacta aacagtctgg gtgaagaaca gcgaattttg
 421 aaccgctcca aaagaggctg ggtttggaat caaatgtttg tcctggaaga gttttctgga
 481 cctgaaccga ttcttgttgg ccggctacac acagacctgg atcctgggag caaaaaaatc
 541 aagtatatcc tatcaggtga tggagctggg accatatttc aaataaatga tgtaactgga
 601 gatatccatg ctataaaaag acttgaccgg gaggaaaagg ctgagtatac cctaacagct
 661 caagcagtgg actgggagac aagcaaacct ctggagcctc cttctgaatt tattattaaa
 721 gttcaagaca tcaatgacaa tgcaccagag tttcttaatg gaccctatca tgctactgtg
 781 ccagaaatgt ccattttggg tacatctgtc actaacgtca ctgcgaccga cgctgatgac
 841 ccagtttatg gaaacagtgc aaagttggtt tatagtatat tggaagggca gccttatttt
 901 tccattgagc ctgaaacagc tattataaaa actgcccttc ccaacatgga cagagaagcc
 961 aaggaggagt acctggttgt tatccaagcc aaagatatgg gtggacactc tggtggcctg
1021 tctgggacca cgacacttac agtgactctt actgatgtta atgacaatcc tccaaaattt
1081 gcacagagcc tgtatcactt ctcagtaccg gaagatgtgg ttcttggcac tgcaatagga
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1201 gatggagatg gaacagcact ttttgaaatc acttctgatg cccaggccca ggatggcatt
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1321 gcagccaatg tccatattga cccacgcttc agtggcaggg ggccctttaa agacacggcg
1381 acagtcaaaa tcgtggttga agatgctgat gagcctccgg tcttctcttc accgacttac
1441 ctacttgaag ttcatgaaaa tgctgctcta aactccgtga ttgggcaagt gactgctcgt
1501 gaccctgata tcacttccag tcctataagg ttttccatcg accggcacac tgacctggag
1561 aggcagttca acattaatgc agacgatggg aagataacgc tggcaacacc acttgacaga
1621 gaattaagtg tatggcacaa cataacaatc attgctactg aaattaggaa ccacagtcag
1681 atatcacgag tacctgttgc tattaaagtg ctggatgtca atgacaacgc ccctgaattc
1741 gcatccgaat atgaggcatt tttatgtgaa aatggaaaac ccggccaagt cattcaaact
1801 gttagcgcca tggacaaaga tgatcccaaa aacggacatt atttcttata cagtctcctt
1861 ccagaaatgg tcaacaatcc gaatttcacc atcaagaaaa atgaagataa ttccctcagt
1921 attttggcaa agcataatgg attcaaccgc cagaagcaag aagtctatct tttaccaatc
1981 ataatcagtg atagtggaaa tcctccactg agcagcacta gcaccttgac aatcagggtc
2041 tgtggctgca gcaatgacgg tgtcgtccag tcttgcaatg tcgaagctta tgtccttcca
2101 attggactca gtatgggcgc cttaattgcc atattagcat gcatcatttt gctgttagtc
2161 atcgtggtgc tgtttgtaac tctacggcgg cataaaaatg aaccattaat tatcaaagat
2221 gatgaagacg ttcgagaaaa catcattcgc tacgatgatg aaggaggagg ggaggaggac
2281 acagaggctt ttgacattgc aactttacaa aatccagatg gaattaatgg atttttaccc
2341 cgtaaggata ttaaaccaga tttgcagttt atgccaaggc aagggcttgc tccagttcca
2401 aatggtgttg atgtcgatga atttataaat gtaaggctgc atgaggcaga taatgatccc
2461 acggccccgc catatgactc cattcagata tatggctatg aaggccgagg gtcagtggct
2521 ggctccctca gctccttgga gtccaccaca tcagactcag accagaattt tgactacctc
2581 agtgactggg gtccccgctt taagagactg ggcgaactct actctgttgg tgaaagtgac
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2701 agggtcactc cccttagata caaccaatgt ggctatttgt tttagaggca agtttagcac
2761 cagtcatcta taaactcaac cacattttaa tgttgaacca aaaaaagata ataaaataaa
2821 aaagtatatg ttaggaggtt ataaatcttg tggagtgtga attaagtatg tggagtgtct
2881 agaagtcctt ggatatttga tatttacctg accaccacag acaaagatt
```

Figure 36

```
  1 MPERLAEMLL DLWTPLIILW ITLPPCIYMA PMNQSQVLMS GSPLELNSLG EEQRILNRSK
 61 RGWVWNQMFV LEEFSGPEPI LVGRLHTDLD PGSKKIKYIL SGDGAGTIFQ INDVTGDIHA
121 IKRLDREEKA EYTLTAQAVD WETSKPLEPP SEFIIKVQDI NDNAPEFLNG PYHATVPEMS
181 ILGTSVTNVT ATDADDPVYG NSAKLVYSIL EGQPYFSIEP ETAIIKTALP NMDREAKEEY
241 LVVIQAKDMG GHSGGLSGTT TLTVTLTDVN DNPPKFAQSL YHFSVPEDVV LGTAIGRVKA
301 NDQDIGENAQ SSYDIIDGDG TALFEITSDA QAQDGIIRLR KPLDFETKKS YTLKVEAANV
361 HIDPRFSGRG PFKDTATVKI VVEDADEPPV FSSPTYLLEV HENAALNSVI GQVTARDPDI
421 TSSPIRFSID RHTDLERQFN INADDGKITL ATPLDRELSV WHNITIIATE IRNHSQISRV
481 PVAIKVLDVN DNAPEFASEY EAFLCENGKP GQMIQTVSAM DKDDPKNGHY FLYSLLPEMV
541 NNPNFTIKKN EDNSLSILAK HNGFNRQKQE VYLLPIIISD SGNPPLSSTS TLTIRVCGCS
601 NDGVVQSCNV EAYVLPIGLS MGALIAILAC IILLLVIVVL FVTLRRHKNE PLIIKDDEDV
661 RENIIRYDDE GGGEEDTEAF DIATLQNPDG INGFLPRKDI KPDLQFMPRQ GLAPVPNGVD
721 VDEFINVRLH EADNDPTAPP YDSIQIYGYE GRGSVAGSLS SLESTTSDSD QNFDYLSDWG
781 PRFKRLGELY SVGESDKET
```

Figure 37

a)

MPERLAEMLLDLWTPLIILWITLPPCIYMAPMNQSQVLMSGSPLELNSLGEEQRILNRS
KRGWVWNQMFVLEEFSGPEPILVGRVLKSVSKLH*

b)

```
      G  R  G  G  A  A  E  A  P  R  A  G  G  G  R  L  L  R  G  Q
3     ggccgcggcggtgcagcagaggcgcctcgggcaggaggagggcggcttctgcgagggcag  62
      P  E  L  H  T  D  L  D  P  G  S  K  K  I  K  Y  I  L  S  G
63    cctgagctacacacagacctggatcctgggagcaaaaaaatcaagtatatcctatcaggt  122
      D  G  A  G  T  I  F  Q  I  N  D  V  T  G  D  I  H  A  I  K
123   gatggagctgggaccatatttcaaataaatgatgtaactggagatatccatgctataaaa  182
      R  L  D  R  E  E  K  A  E  Y  T  L  T  A  Q  A  V  D  W  E
183   agacttgaccgggaggaaaaggctgagtataccctaacagctcaagcagtggactgggag  242
      T  S  K  P  L  E  P  P  S  E  F  I  I  K  V  Q  D  I  N  D
243   acaagcaaacctctggagcctccttctgaatttattattaaagttcaagacatcaatgac  302
      N  A  P  E  F  L  N  G  P  Y  H  A  T  V  P  E  M  S  I  L
303   aatgcaccagagtttcttaatggaccctatcatgctactgtgccagaaatgtccattttg  362
      G  T  S  V  T  N  V  T  A  T  D  A  D  D  P  V  Y  G  N  S
363   ggtacatctgtcactaacgtcactgcgaccgacgctgatgacccagtttatggaaacagt  422
      A  K  L  V  Y  S  I  L  E  G  Q  P  Y  F  S  I  E  P  E  T
423   gcaaagttggtttatagtatattggaagggcagccttatttttccattgagcctgaaaca  482
      A  I  I  K  T  A  L  P  N  M  D  R  E  A  K  E  E  Y  L  V
483   gctattataaaaactgcccttccaacatggacagagaagccaaggaggagtacctggtt  542
      V  I  Q  A  K  D  M  G  G  H  S  G  G  L  S  G  T  T  T  L
543   gttatccaagccaaagatatgggtggacactctggtggcctgtctgggaccacgacactt  602
      T  V  T  L  T  D  V  N  D  N  P  P  K  F  A  Q  S  L  Y  H
603   acagtgactcttactgatgttaatgacaatcctccaaaatttgcacagagcctgtatcac  662
      F  S  V  P  E  D  V  V  L  G  T  A  I  G  R  V  K  A  N  D
663   ttctcagtaccggaagatgtggttcttggcactgcaataggaagggtgaaggccaatgat  722
      Q  D  I  G  E  N  A  Q  S  S  Y  D  I  I  D  G  D  G  T  A
723   caggatattggtgaaaatgcacagtcatcatatgatatcatcgatggagatggaacagca  782
      L  F  E  I  T  S  D  A  Q  A  Q  D  G  I  I  R  L  R  K  P
783   ctttttgaaatcacttctgatgcccaggcccaggatggcattataaggctaagaaaacct  842
      L  D  F  E  T  K  K  S  Y  T  L  K  V  E  A  A  N  V  H  I
843   ctggactttgagaccaaaaaatcctatacgctaaaggtagaggcagccaatgtccatatt  902
      D  P  R  F  S  G  R  G  P  F  K  D  T  A  T  V  K  I  V  V
903   gacccacgcttcagtggcaggggggccctttaaagacacggcgacagtcaaaatcgtggtt  962
      E  D  A  D  E  P  P  V  F  S  S  P  T  Y  L  L  E  V  H  E
963   gaagatgctgatgagcctccggtcttctcttcaccgacttacctacttgaagttcatgaa 1022
      N  A  A  L  N  S  V  I  G  Q  V  T  A  R
1023  aatgctgctctaaactccgtgattgggcaagtgactgctcgt etc.....
```